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| 09/932,370 | 08/17/2001 | Mitchell Shirvan | 62812-A/JPW/GJG/CSN | 4884 |

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| EXAMINER | |
|---|---|
| HUI, SAN MING R | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | 5 |

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/932,370 | Applicant(s) SHIRVAN ET AL. | |
|---|---|---|---|
| | Examiner San-ming Hui | Art Unit 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. §.133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-45,47-53,55-77,79-91 and 93-105* is/are pending in the application.

4a) Of the above claim(s) *4,5,25,28,29,50,51,74 and 75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-24,26,27,30-45,47-49,52,53,55-73,76,77,79-91 and 93-105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Applicant's amendments filed April 4, 2003 have been entered. The cancellation of claims 46, 54, 78, and 92 in the response filed April 4, 2003 is acknowledged. The addition of claims 97-105 in the response filed April 4, 2003 is acknowledged.

Claims 1-45, 47-53, 55-77, 79-91, and 93-105 are pending.

Applicant's election with traverse of the specie, N-(2-n-propylpentanoyl) glycinamide, in Paper No. 6 is acknowledged.

Claims 4, 5, 25, 28, 29, 50, 51, 74, and 75 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected specie, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 6.

Claims 1-3, 6-24, 26, 27, 30-45, 47-49, 52-53, 55-73, 76-77, 79-91, and 93-105 have been examined herein to the extent they read on the elected invention and species.

The outstanding rejections under 35 USC 112, first are withdrawn in view of the amendments filed April 4, 2003.

The outstanding rejections of claims 47 and 94 under 35 USC 112, first are withdrawn in view of the amendments filed April 4, 2003

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 101-103 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The method of employing the herein claimed compound to treat the pain disorders recited in claims 101-103 is not supported by the instant specification. Page 2 in the instant specification discloses the Background of the Invention and general teachings with regard to various types of pain. There is no teachings or suggestions that the herein claimed compounds are effective in treatment or prophylaxis of the herein claimed pain disorders in page 2 of the instant specification. Applicant is required to cancel the new matter presented in the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 96-101 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression, "a method of preventing pain" in claim 96, renders the claims indefinite as failing to clearly set forth the metes and bounds of the patent protection desired. Examples of how and when to prevent pain are not set forth in the

specification. The only example discussing preventing of pain is experimental example 2, page 17-19 in the instant specification. However, this example only demonstrates the efficacy of treating allodynia (a painful condition) when the animals have already suffered from pain. No example is set forth in the instant specification on prevention of pain by employing the herein claimed compounds before pain occurred. Absent such exemplication, the skilled artisan could not establish the identity of those situations wherein prevention of pain would be effected. Furthermore, it is unclear as to the degree of prevention (e.g., total prevention, some prevention, probable prevention, total prevention in most cases...etc.) herein because the specification does not disclose the extent of prevention achieved. Examiner would favorably consider the term "prophylaxis" over "prevention".

The expression "miscellaneous-type headache" recited in claims 97-100 renders the claims indefinite as to the headache encompassed by the claims. It is not clear what the term "miscellaneous-type headache" referred to.

The expression "phantom pain" recited in claim 101 renders the claim indefinite because phantom pain is a neuropathic pain, not a somatogenic pain.

The expression "HIV pain" recited in claim 101 renders the claim indefinite because it is not clear what kind of pain "HIV pain" encompasses.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 6-24, 26, 27, 30-45, 47-49, 52-53, 55-73, 76-77, 79-91, and 93-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bialer et al. (US Patent 5,585,358 from the IDS received April 22, 2002) in view of Hansen (Southern Medical Journal, 1999;92(7):642-649), McQuay et al. (BMJ, 1995;311:1047-1052), Shank et al. (US Patent 5,760,007), Carrazana et al. (US Patent 6,319,903), Magnus (Epilepsia, 1999;40(Suppl 6):S66-S72), Zakrzewska et al. (Pain 1997;73(2):233-230), and Merck Manual (16th ed., 1992, page 1412).

Bialer et al. teaches the elected compound, N-(2-n-propylpentanoyl) glycinamide, is useful as anticonvulsant for treating epilepsy and other neurological disorders (see the abstract, and col. 7, line 23-44, Example 1; col. 13, line 4 – col.17, line 34). Bialer et al. teaches the effective dose in a composition for N-(2-n-propylpentanoyl) glycinamide as 10 to about 500mg (col. 3, line 59-61). Bialer et al. also teaches the $ED_{50}$ dosage of N-(2-n-propylpentanoyl) glycinamide for antiepileptic activities as 73mg/kg (about 5000mg in an 70kg adult) (See col. 13, line 39). Bialer et al. also teaches N-(2-n-

propylpentanoyl) glycinamide can be administered through oral, intravenous, intraperitoneal, intramuscular, and topical (See col. 7, line 10-14). Bialer et al. also teaches those skilled in the art would be able to determine the precise effective amount and routes of administration of the herein compound to be administered (See col. 6, line 49-59).

Bialer et al. does not expressly teach N-(2-n-propylpentanoyl) glycinamide to be useful as treating or preventing acute, chronic, neuropathic pain, or cancer pain. Bialer et al. does not expressly teach the dosage of N-(2-n-propylpentanoyl) glycinamide as 6000mg or 3000mg. Bialer et al. does not expressly teach the route of administration as intranasal, sublingual, inhalation, buccal, intravaginal, and pulmonary. Bialer et al. does not expressly teach the dosing frequency of N-(2-n-propylpentanoyl) glycinamide as periodic six times daily.

Hansen teaches various antiepileptic agents are useful in treating both acute and chronic pain (See page 642, col. 2, second paragraph, page 646, col. 2, fourth paragraph to page 647, whole page).

McQuay et al. teaches the effectiveness of various anticonvulsants such as carbamazeoine, phenytoin, Valproate sodium are effective in treating neuropathic pain such as trigeminal neuralgia, cancer pain, rheumatoid arthritis and migraine prophylaxis in various degree (See the abstract, Tables 1-4, also Section Trigeminal neuralgia and Migraine prophylaxis).

Shank et al. teaches topiramate, an anticonvulsant, is useful in treating neuropathic pain (See claim 2).

Carrazana et al. teaches topiramate, an anticonvulsant, is useful in treating cluster headaches (See claims 1-15).

Magnus teaches gapapentin, an anticonvulsant, is useful in treating neuropathic pain and useful in migraine prophylaxis (See Summary, also page S66 to S68, first col. Second paragraph; also page S71, Table 5).

Zakrzewska et al. teaches lamotrigine, an anticonvulsant, is useful in treating trigeminal neuralgia, a neuropathic pain. (See the abstract).

Merck Manual teaches that peripheral neuropathy pain is associated with tumor infiltration, which is a neuropathic pain (See page 1412).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ N-(2-n-propylpentanoyl) glycinamide, in the herein claimed dosage and dosing regimen, in a method of treating and prophylaxis pain. It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer N-(2-n-propylpentanoyl) glycinamide in the herein claimed routes of administration.

One of ordinary skill in the art would have been motivated to employ N-(2-n-propylpentanoyl) glycinamide, in the herein claimed dosage and dosing regimen, in a method of treating and prophylaxis pain. Based on the cited prior art, antiepileptic compounds with vastly different structure and mechanism of actions are useful for treating and preventing neuropathic pain, migraine headache and cluster headache. The only common property of these antiepileptic compounds is that they are all useful as anticonvulsant. Therefore, employing any known anticonvulsant, including the N-(2-

n-propylpentanoyl) glycinamide, would have been reasonably expected to be useful to treat or prevent neuropathic pain such as peripheral neuropathic pain associated with tumor infiltration, migraine headache and cluster headache. Furthermore, the optimization of result effect parameters (e.g., dosage range, dosing regimens) is obvious as being within the skill of the artisan, based on the teachings of Bialer et al. (See col. 6, line 49-59).

One of ordinary skill in the art would have been motivated to administer N-(2-n-propylpentanoyl) glycinamide in the herein claimed routes of administration because one of ordinary skill in the art would be charge to possess all the conventional method of administering a therapeutic compound. Selecting the herein claimed routes of administration over the obvious alternatives would be considered obvious as being within the purview of a skilled artisan, absent evidence to the contrary.

***Response to Arguments***

Applicant's arguments filed April 4, 2003 averring the cited prior art's failure to teach the method of treating pain recited in claims 101-103 have been fully considered but they are not persuasive. As discussed in the rejection set forth above, various antiepileptic agents are known to treat neuropathic pain such as trigeminal neuralgia and peripheral neuropathy. Therefore, employing antiepileptic agent such as the instant compound would be reasonably expected to be similar effective.

Applicant's arguments filed April 4, 2003 averring the cited prior art's failure to teach the dosage herein claimed have been fully considered but they are not

persuasive. As discussed above, Bialer et al. also teaches the $ED_{50}$ dosage of N-(2-n-propylpentanoyl) glycinamide for antiepileptic activities as 73mg/kg (about 5000mg in an 70kg adult) (See col. 13, line 39). As anyone of ordinary skill in the art will appreciate, preferred dosages are merely exemplary and serve as useful guideposts for the physician. There are, however, many reasons for varying dosages, including by orders of magnitude; for instance, an extremely heavy patient or one having an unusually severe infection would require a correspondingly higher dosage. Furthermore, it is routine during animal and clinical studies to dramatically vary dosage to obtain data on parameters such as toxicity. Therefore, the optimization of result effect parameters (e.g., dosage range, dosing regimens) is obvious as being within the skill of the artisan, based on the teachings of Bialer et al., absent evidence to the contrary.

Applicant's arguments filed April 4, 2003 averring valproate not effective in alleviating cluster headaches and therefore no motivation is provided by the cited prior art have been fully considered but they are not persuasive. The cited prior art, as a whole, teaches that various structurally different anticonvulsants are useful in treating or prophylaxis of neuropathic pain. It is known that a particular anticonvulsant is effective in treating one type of neuropathic pain while may be ineffective or less effective in treating other kinds of neuropathic pain (See e.g., McQuay, page 1049, valproate sodium is useful in migraine prophylaxis, while is not good for acute postoperative pain). It is also known that in a clinical study, there must be some non-responders in the treatment group and some responders in the placebo group (See e.g., McQuay, page 1049, the analgesic outcome column, note that there is no 100% response or non-

response rate in neither the treatment group nor the placebo group). Therefore, merely pointing out one or two cases that certain anticonvulsants are not effective for treating a specific neuropathic pain such as cluster headache in that particular individual is not sufficient to overcome the rejection since it is well expected by one of ordinary skill in the art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
June 13, 2003

SREENI PADMANABHAN
PRIMARY EXAMINER

6/16/03